

Impact of Month of Birth on the Development of Autoimmune Thyroid Disease in the United Kingdom and Europe

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Context: Viral/bacterial infection is proposed as a trigger for the autoimmune thyroid diseases (AITD): Graves' disease (GD) and Hashimoto's thyroiditis (HT). Previous studies in European Caucasian AITD subjects found higher birth rates in the autumn/winter, suggesting those born in the autumn/winter experience increased viral/bacterial exposure after birth, impacting upon immune system development and predisposing to AITD later in life.

Objective: Month of birth effects were investigated in three independent European Caucasian AITD datasets.

Design: Variation in GD and HT onset was compared across months and seasons, with fluctuations across all 12 months analyzed using a Walter-Elwood test.

Setting: The study was conducted at a research laboratory.

Patients: National UK Caucasian AITD Case Control Collection (2746 GD and 502 HT compared with 1 423 716 UK births), National UK Caucasian GD Family Collection (239 GD and 227 unaffected siblings), and OXAGEN AITD Caucasian Family Collection (885 GD, 717 HT, and 794 unaffected siblings of European Caucasian descent).

Main Outcome Measures: Case-control and family-based association studies were measured.

Results: No consistent month of birth effects were detected in GD females or males across all three collections. In HT females from the OXAGEN AITD Caucasian Family Collection, slightly higher birth rates were detected in autumn (Walter's test statistic = 7.47, $P = .024$) however, this was not seen in the HT females from the case-control cohort.

Conclusion: Our results suggest in UK/Northern European Caucasian GD subjects, month of birth does not impact on AITD development. Although some month of birth effects for HT females in one collection cannot be excluded, only further work in larger European Caucasian AITD collections can confirm these effects. (*J Clin Endocrinol Metab* 99: E1459–E1465, 2014)

ISSN Print 0021-972X ISSN Online 1945-7197

Printed in U.S.A.

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Received January 29, 2014. Accepted May 9, 2014.

First Published Online May 19, 2014

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Abbreviations: AITD, autoimmune thyroid diseases; CI, confidence interval; GD, Graves' disease; HT, Hashimoto's thyroiditis; OR, odds ratio; T1D, type 1 diabetes.

Viral/bacterial infection is proposed as a key environmental trigger for the common autoimmune thyroid diseases (AITD), Graves' disease (GD) and Hashimoto's thyroiditis (HT) (1, 2). Several mechanisms have been proposed to explain viral/bacterial triggering of AITD, including molecular mimicry and viruses/bacteria acting as superantigens (2). Interestingly, *Enterovirus* infection during gestation and after birth is proposed to play a role in type 1 diabetes (T1D) onset and other autoimmune diseases (3–5), suggesting viral/bacterial exposure during gestation or early in life could alter immune system development, predisposing to autoimmune disease later in life. Further support for this hypothesis comes from variation in seasonality of birth rates observed in many autoimmune conditions compared with the general population (6, 7). In AITD, Krassas et al (8) investigated month of birth in 359 Greek GD and 664 HT patients compared with 37 119 general population births. Greek GD female birth rates peaked in the spring/autumn, GD male birth rates peaked in the winter, HT female birth rates peaked in the winter, and HT male birth rates peaked in the winter/summer (8), which varied from the general Greek population in which female and male birth rates peaked in the summer. This suggests birth rates of AITD patients are increased in the autumn/winter months when viral/bacterial load is highest. Although several studies have investigated month of birth effects in T1D, multiple sclerosis, and celiac disease (9–11), only limited work has been performed to investigate a possible role for month of birth effects in AITD. The aim of this study was to investigate whether alterations in month of birth was impacting upon AITD onset in UK and European Caucasian populations by looking at seasonality of birth rates in a large AITD case-control collection and two independent Caucasian family collections.

Materials and Methods

Subjects

Month of birth effects were analyzed within the National UK Caucasian AITD Case Control Collection (2281 GD females, 465 GD males, 433 HT females, and 69 HT males) compared against 1 423 716 UK births from 1956 through 1957 (12). Samples were recruited from centers in Birmingham, Bournemouth,

Cambridge, Cardiff, Exeter, Leeds, Sheffield, and Newcastle, United Kingdom (see Supplemental Methods for further information on recruitment criteria). Month of birth was also examined within two family collections. The National UK Caucasian GD Family Collection (206 GD females, 33 GD males, 132 unaffected female siblings, and 95 unaffected male siblings) were recruited from the same centers as the National UK Caucasian AITD Case Control Collection (see Supplemental Methods). The OXAGEN AITD Caucasian Family Collection (762 GD females, 123 GD males, 632 HT females, 85 HT males, 460 unaffected female siblings, and 334 unaffected male siblings) were collected from centers in the United Kingdom (Birmingham, Cambridge, Glasgow, Oxford, and Sheffield), Denmark, and The Netherlands (12, 13) (see Supplemental Methods for further information on recruitment criteria and geographical location of centers contributing to these collections). Because AITD exhibits a strong female preponderance, all month-of-birth-data were split by gender.

Data extraction and analysis

Month-by-month variation was screened using χ^2 or Fisher's exact tests, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated to determine the differences in birth rates for each month between GD or HT cases and the UK general birth rate (case-control collection) or unaffected siblings (family collections). Data were also split by season of birth (Supplemental Figures 1–3), and further χ^2 /Fisher's exact tests were performed. To estimate within-year fluctuations for a 12-month periodicity (simple harmonic seasonal variation), the Walter-Elwood test for seasonality was used to determine the differences in the month-of-birth distribution across all 12 months ($P < .05$, Walter-Elwood test statistic > 5.991 were significant).

Results

National UK Caucasian AITD Case Control Collection

When comparing month-of-birth rates in GD females from the National UK AITD Caucasian Case Control Collection against the general UK population, no significant difference in birth rate across months, seasons, or fluctuations across the whole 12-month period was detected (Walter's test statistic = 2.71, $P = .26$) (Figure 1 and Supplemental Figure 1). In GD males, increased birth rates in July ($P = .03$, OR 1.39, 95% CI 1.04–1.85) and reduced birth rates in September ($P = .01$, OR 0.59, 95% CI 0.39–0.90) and November ($P = .03$, OR 0.65, 95% CI

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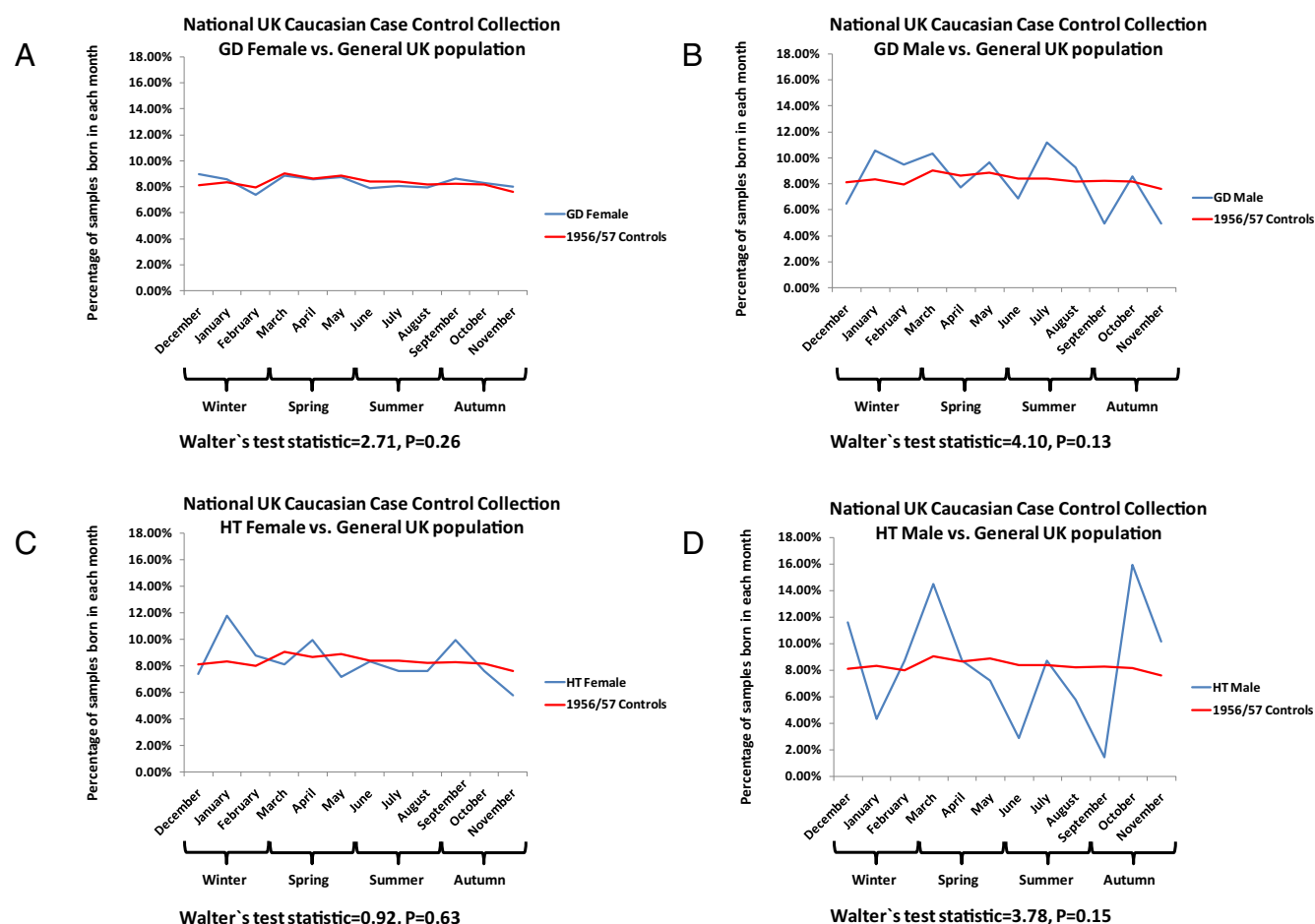


Figure 1. Month-of-birth distribution for National UK Caucasian AITD Case Control Collection. The National UK Caucasian AITD Case Control Collection consisted of UK Caucasian GD and HT patients collected from specialist clinics across the United Kingdom in Birmingham, Bournemouth, Cambridge, Cardiff, Exeter, Leeds, Sheffield, and Newcastle, which were compared against the UK general population live births from 1956 through 1957 (see Supplemental Methods for details on recruitment criteria used for each collection). A, Female GD month of birth compared against the general UK population month of birth. B, Male GD month of birth compared against the general UK population month of birth. C, Female HT month of birth compared against the general UK population month of birth. D, Male HT month of birth compared against the general UK population month of birth.

0.42–0.98) were detected (Figure 1 and Supplemental Figure 1). Seasonal analysis supported the monthly analysis, revealing lower birth rates in autumn for GD males ($P = .005$, OR 0.72 95% CI 0.57–0.91). When looking at birth rates across the whole 12-month period, no significant fluctuations were detected (Walter's test statistic = 4.10, $P = .13$) (Figure 1).

Within HT females, higher birth rates were seen in January ($P = .009$, OR 1.48, 95% CI 1.11–1.99) (Supplemental Figure 1); however, no seasonal differences or fluctuations in birth rates across the 12-month period were detected (Walter's test statistic = 0.92, $P = .63$) (Figure 1 and Supplemental Figure 1). In HT males, a decreased birth rate was seen in September ($P = .04$, OR 0.24, 95% CI 0.03–1.75); however, the 95% CI crossed OR 1.00, suggesting caution when interpreting this result. Higher birth rates were also detected in October ($P = .02$, OR

2.21, 95% CI 1.16–4.20) for HT males (Supplemental Figure 1). This was not supported by seasonal analysis or when looking at fluctuations across all 12 months in HT males (Walter's test statistic = 3.78, $P = .15$) (Figure 1).

National UK Caucasian GD Family Collection and OXAGEN AITD Caucasian Family Collection

A downside of using case-control collections to look at month-of-birth effects is the difficulty of matching cases to the general population. The advantage of looking within families is that AITD patients and their unaffected siblings have been exposed to similar environments, reducing the impact of nonshared environmental factors on month-of-birth effects. As a complementary approach to looking at month of birth within the National UK Caucasian AITD Case Control Collection, month of birth was also screened within two independent Caucasian AITD family collections.

When looking at month-of-birth effects within the National UK Caucasian GD Family Collection female and male GD cases compared against unaffected female and male siblings, respectively, no variation in month, season, or fluctuations across the whole 12-month period were detected (Walter's test statistic = 3.35–3.80, $P = .15$ – 0.19) (Figure 2 and Supplemental Figure 2). This did not support the previously detected increase in autumn births seen in GD males within the case-control collection.

Month-of-birth effects were also examined within the OXAGEN AITD Caucasian Family Collection. When looking at GD females and males compared with unaffected females and male siblings, respectively, no significant differences in month, season, or fluctuations across the whole 12-month period were detected (Figure 2 and Supplemental Figure 3). When looking at month-of-birth fluctuations across all 12 months in HT females, greater birth rates in winter/autumn and lower birth rates in spring/summer relative to unaffected female siblings were seen (Walter's test statistic = 7.47, $P = .024$) (Figure 2). However, when looking at monthly or seasonal effects, no significant differences were detected, suggesting this was not being driven by a given month or season but by variation across the whole period (Supplemental Figure 3). A different picture emerged in HT males, with monthly analysis revealing a weak increase in birth rates for HT males in January compared with unaffected males ($P = .04$, OR 2.02, 95% CI 1.02–4.02) (Supplemental Figure 3). However, no variation in season or fluctuations across the whole 12-month period were detected (Walter's test statistic = 1.75, $P = .42$) (Figure 2 and Supplemental Figure 3).

When combining gender in each collection, no variation in month, season, or fluctuation across all 12 months was detected in GD or HT across all three collections (data not shown).

Discussion

Screening month-of-birth effects in a large UK Caucasian AITD Case Control Collection and two independent AITD family collections, one of UK Caucasian descent and one of European Caucasian descent, detected no consistent association for a role of month of birth across the three collections. GD females, the largest AITD subgroup, showed no month-of-birth effects in any of the three collections. For GD males, some differences in month of birth and reduction in GD males born in autumn were detected in the National UK Caucasian AITD Case Control Collection. However, when looking at fluctuation across all 12 months, no change in birth rate distribution was seen.

No variation in month, season, or fluctuation across the 12-month period was seen in the two independent GD family collections, suggesting that this decrease in GD male birth rate in autumn within the case-control collection should be viewed with caution.

Some evidence for variation in monthly birth rates was seen in HT males from the National UK Caucasian AITD Case Control Collection and the OXAGEN AITD Caucasian Family Collection but could be due to the small number of HT males in both collections (69 and 85 males, respectively). In HT females from the National UK Caucasian AITD Case Control Collection, a significant increase in birth rates in January was detected; however, no seasonal differences or fluctuations across the whole 12-month period were found. Data from the OXAGEN AITD Caucasian Family Collection revealed fluctuation in birth rates across the 12-month period within HT females compared with unaffected siblings. Birth rates across all autumn/winter months, except December, were higher in HT females relative to unaffected female siblings in whom the birth rates peaked in May (spring) and August (summer). Month-by-month analysis showed that variation was not being driven by a specific month, suggesting subtle changes across all 12 months contributed to differences in birth rates detected by the Walter-Elwood test. This could suggest that in the OXAGEN AITD Caucasian Family Collection, variation in month of birth could be playing a role in female HT onset.

There are several potential reasons that we found month of birth effects only for HT females in our OXAGEN AITD Caucasian Family Collection. Variation in seasonal temperatures, infection rates, and improving hygiene across years/decades presents challenges when assessing the long-term impact of environmental factors on AITD. The broad spectrum of symptoms used to diagnose GD and HT may dilute out a subset of patients whose pathology was associated with month of birth. When looking at UK infection rates for viruses and bacteria linked with AITD, *Adenovirus* shows peak infection rates in winter/spring, whereas *Yersinia* and *Paravirus B14* show a peak incidence in spring/summer in the United Kingdom, whereas *Cytomegalovirus*, *Epstein-Barr*, and *Hepatitis C* do not show seasonal variation (<http://www.hpa.org.uk>) (14–16), suggesting these infections are unlikely to contribute to autumn/winter month of birth effects. The use of UK monthly birth rate data from 1956 through 1957 to represent the general UK population birth rate could be impacting upon our results due to possible effects of polio, Asian flu and Bornholm disease (caused by *Coxsackie B*) epidemics during this time (<http://www.hpa.org.uk>) (17) or by masking localized peaks of infection present in the locations that contributed to our

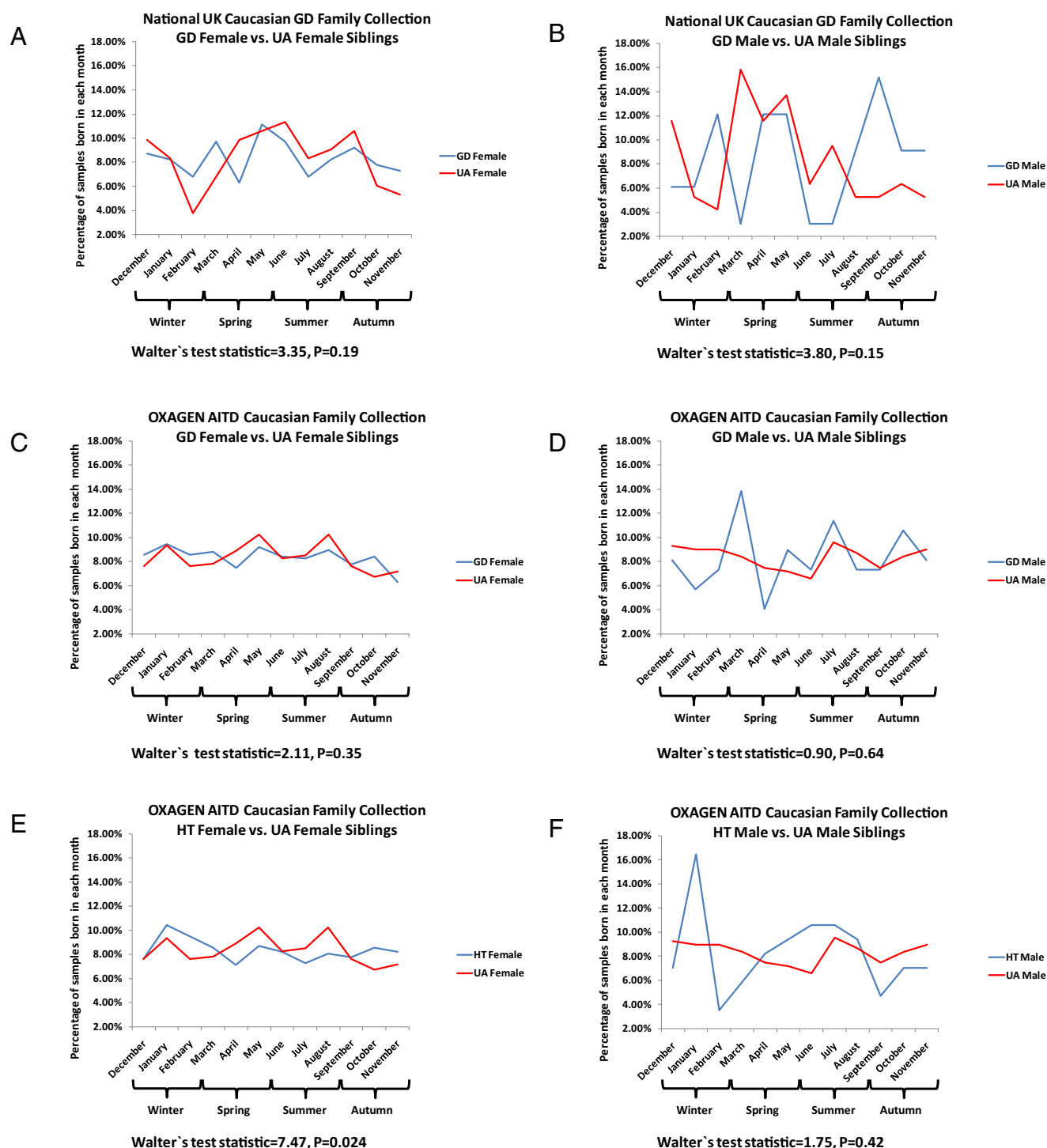


Figure 2. Month-of-birth distribution within the National UK Caucasian GD Family collection and OXAGEN AITD Caucasian Family Collection. The National UK Caucasian GD Family collection consisted of UK Caucasian GD patients and their unaffected siblings recruited from specialist clinics across the United Kingdom, including Birmingham, Bournemouth, Cambridge, Cardiff, Exeter, Leeds, Sheffield, and Newcastle. The OXAGEN AITD Caucasian Family Collection consisted of Caucasian GD and HT patients and their unaffected siblings recruited from specialist clinics across the United Kingdom, including Birmingham, Cambridge, Glasgow, Oxford, and Sheffield, Denmark, and The Netherlands (see Supplemental Methods for further details on recruitment criteria and geographical location of samples within each collection). A, National UK Caucasian GD Family collection female GD index cases month of birth compared against UA female siblings month of birth. B, National UK Caucasian GD Family collection male GD index cases month of birth compared against UA male siblings month of birth. C, OXAGEN AITD Caucasian Family Collection female GD month of birth compared against female UA siblings month of birth. D, OXAGEN AITD Caucasian Family Collection male GD month of birth compared against male UA siblings month of birth. E, OXAGEN AITD Caucasian Family Collection female HT month of birth compared against female UA siblings month of birth. F, OXAGEN AITD Caucasian Family Collection male HT month of birth compared against male UA siblings month of birth. UA, unaffected.

case-control collection. Although some of the OXAGEN AITD Caucasian Family Collection and our other collections were recruited from the same geographical locations in the United Kingdom, including Birmingham and Sheffield (with no overlap in patients between collections), the OXAGEN collection also contained patients recruited from different geographical locations, including samples from Cambridge, Glasgow, and Oxford in the United Kingdom, Denmark, and The Netherlands (Supplemental Methods). It is also important to note that no correction for multiple testing was applied, which could possibly explain associations within some collections.

There has been much debate over whether month-of-birth effects are actually a surrogate marker for date of conception/gestational effects. In T1D, rotavirus infection and subsequent antibody development in the mother during gestation has been linked with pancreatic damage in the fetus (18). Antibodies generated against maternal viral/bacterial infection may be more likely to cross the placenta and cause autoimmune attack against the developing fetus' pancreas rather than the thyroid gland, possibly explaining why we did not detect consistent month-of-birth effects across our AITD collections. Vitamin D deficiency, which affects the immune system development during pregnancy (19, 20), is also more prevalent during the autumn/winter months, suggesting month-of-birth effects could be a surrogate marker for this condition. Although impossible to access environmental impact before birth in AITD patients, it is possible that HT females in the OXAGEN AITD Caucasian Family Collection could have encountered a specific combination of environmental triggers during gestation or after birth in the autumn/winter months that impacted upon the development of their immune systems and predisposed them to AITD, whereas HT females in the other collections did not.

In conclusion, this study shows that in our UK and Northern European Caucasian GD collections, month or season of birth is unlikely to be exerting a significant impact on disease development. Although some month-of-birth effects for HT females in one collection cannot currently be ruled out, further work in larger Caucasian AITD collections across Europe is required to confirm whether month of birth plays any role in AITD.

Acknowledgments

We thank all the principal investigators, doctors, and nurses for recruiting AITD subjects into the National UK Caucasian AITD Case Control Collection and the National UK Caucasian GD Family Collection. We also thank all the families with AITD who

kindly agreed to participate in the OXAGEN AITD Caucasian Family Collection and all the research nurses who assisted with the recruitment of families.

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National UK Caucasian AITD Case Control Collection and National UK Caucasian GD Family Collection were funded by the Wellcome Trust Grant 068181.

Disclosure Summary: The authors have nothing to declare.

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